29, 1998, which claims priority of United States provisional patent applications no. 60/058,170, filed May 30, 1997, and no. 60/048,381, filed June 3, 1997.---

IN THE CLAIMS:

Cancel claim 29, and amend claim 15 to read as shown below. A marked-up version of this claim indicating the changes made by this amendment is shown on the last page of this paper.

15. (amended) A method of monitoring transplanted material in a patient, comprising:

a) providing a urine sample suspected of containing nucleic acid of the transplanted material, which transplanted material is located outside of the urinary tract; and

b) analyzing said urine sample for nucleic acids from the cell genome of the transplanted material that are different from nucleic acids of the recipient and that have crossed the kidney barrier.

IN THE DRAWINGS:

Appropriate substitute figures will be presented when allowed claims are indicated.

REMARKS

Support for the wording added to claim 15 appears in the specification at page 5, lines 13-14 (transplanted material located outside of the urinary tract) and page 32, line 5 (nucleic acids ... that are different from nucleic acids of the recipient). No new matter is presented by this amendment.

Claim Rejections – 35 U.S.C. §112

The above amendment is made in response to the rejection under 35 U.S.C. §112, second paragraph. Claim 15 as amended does not extend to nucleic acid from transplanted kidney cells. The claim was already limited to nucleic acids that have crossed the kidney barrier, thereby excluding transplanted kidney cells, and with the present amendment the claim is expressly limited to the detection of nucleic acids from transplanted material that is located outside the urinary tract,

further emphasizing that nucleic acids from transplanted kidney cells are not included wihtin the scope of the claim. Reconsideration of this rejection is therefore respectfully requested.

Claim Rejections – 35 U.S.C. §102/103

The rejections of claims 15-19, 21 and 22 over Lisby et al., and claims 19-23 over Schatzl et al. are respectfully traversed.

Transplanted material does not include viruses, and hence the claims do not cover viral DNA. In addition, the viral DNA that may appear in the urine according to the Lisby et al. and Schatzl et al. disclosures and the disclosures of other researchers do not reach the urine by crossing the kidney barrier, and are excluded from Applicants' claims for this reason as well. The DNA that appears in the urine is DNA from kidney cells or from cells lining the bladder. The cells of the bladder can be infected by many different viruses, whose DNA will then enter the urine directly, without the need to cross the kidney barrier.

Both cytomegalovirus (CMV) and polyomavirus (PV, of which the two known strains are BKV and JCV) infect cells of the kidney, bladder and urethra. Due to the activity of the immune system, the infection is usually dormant and undetectable. In immunocompromised patients, however, these viruses become reactivated. Immunocompromise occurs during transplantation procedures, since these procedures are accompanied by intensive immunosuppression to prevent rejection of the transplanted material. Secondary infection is rare but also leads to infection of the urinary tract. Thus, the major sources of viral DNA-containing particles in the urine are cells that are shed from the urinary tract lysis of urinary tract cells. This is borne out by the references cited as well as the literature cited in the enclosed Information Disclosure Statement.

The Lisby et al. and Schatzl et al. references cited in the Office Action both report analyses performed after transplantations. The Prosch et al. paper cited in the IDS likewise reports analyses performed after liver, kidney, heart, or bone transplantation. The Nickeleit et al. paper cited in the IDS explains that "in healthy individuals, PV resides in a latent state in the kidney (page 1081, 3d paragraph); and "In immunocompromised patients, PV can cause a morphologically manifest renal infection ... In native and transplanted kidneys, PV (BK virus strain) is found in areas of interstitial nephritis" (page 1081, 4th paragraph). The authors found "Intranuclear viral inclusion bodies in epithelial cells along the entire nephron and the transitional cell layer ..." and "All patients

were excreting PV-infected cells in the urine" (pages 1080-1081, Abstract, and page 1084 in the paragraph under the heading "Decoy Cells in the Urine")).

Another potential source of BK and JC viruses in the urine is hemorrhagic cystitis that often accompanies bone marrow transplantation and is supposedly initiated by polyomavirus, as reported in the Chan et al. and Bedi et al. papers included in the IDS.

To summarize, neither Lisby et al. not Schatzl et al. disclose the detection of DNA that from transplanted material. The viruses and viral DNA that they detect in urine did not reach the urine by crossing the kidney barrier. Instead, they were already present in the kidney in a dormant state and were activated by the immunosuppression that accompanies the transplantation procedure. This distinguishes the invention as claimed from the disclosures of these references since claim 15, the sole independent claim remaining in this application, is expressly limited to nucleic acids from the cell genome of the transplanted material and that have crossed the kidney barrier. These references do not suggest that nucleic acids from transplanted material outside of the urinary tract will cross the kidney barrier and be detectable in the urine. Applicants' claims are therefore both novel and nonobvious over the disclosures of these references.

The remaining rejections and citations in the Office Action are directed to claims that are either dependent on claim 15 or to canceled claim 29. Accordingly, further discussion is not necessary, and the distinctions expressed above apply to these rejections as well.

In view of the foregoing, Applicants respectfully submit that all claims now pending in this Application recite patentable subject matter meeting all requirements of 35 U.S.C. Should any matters remain that can be resolved by a telephone conference, the examiner is encouraged to contact Applicants' attorney (the undersigned) at the telephone number indicated below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

15. (amended) A method of monitoring transplanted material in a patient, comprising:

a) providing a urine sample suspected of containing nucleic acid **of the** [from] transplanted material**, which transplanted material is located outside of the urinary tract**; and

b) analyzing said urine sample for **nucleic acids** [a nucleic acid sequence] **from the cell genome of the transplanted material that are different from nucleic acids of the recipient and** that **have** [has] crossed the kidney barrier [and that was not present in the patient prior to transplantation].